

Is nutraceutical supplementation appropriate for COVID-19 management?

Recently, now that coronavirus disease 2019 (COVID-19) vaccines are becoming available for the ultimate prevention of COVID-19 infection, a discussion has begun on another level of global management of the disease based on the hypothesis that an individual's dietary status may play an important adjunctive role in protective immunity against this devastating disease.¹ Populations in European countries with lower death rates were found to have diets that consisted of fermented vegetables or cabbage.^{2,3} Presented in Fig. 1 are the current death rates per million people of various western and eastern European countries that show lower rates in Germany, Austria, the Czech Republic, Poland, Slovakia, the Baltic states, and Finland, countries with populations that have a common feature of eating large quantities of fermented foods in contrast to Belgium, France, Italy, Spain, and the United Kingdom, with populations whose diets contain lower quantities of fermented foods and with higher mortality rates.¹

WHAT ARE SOME EXPLANATIONS FOR MITIGATION OF COVID-19 MORTALITY BY DIETARY FACTORS?

As a result of binding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to its angiotensin-converting enzyme 2 receptor, angiotensin-converting enzyme 2 is downregulated and the angiotensin II receptor type 1 axis is reciprocally activated, which leads to the production of a family of highly reactive oxygen molecules known as reactive oxygen species responsible for oxidative stress.³ This leads to two of the severest outcomes of COVID-19 infection, *i.e.*, insulin resistance and lung and endothelial damage. In humans, the most potent antioxidant that can block the angiotensin II receptor type 1 axis is the nuclear factor (erythroid-derived 2) like 2 (Nrf2), a transcription factor that regulates the

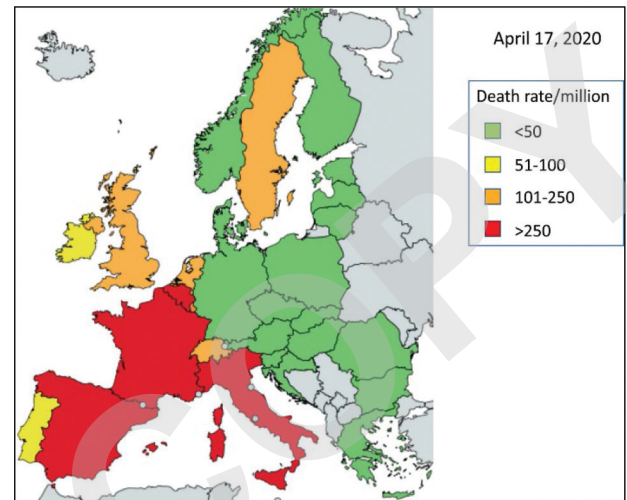


Figure 1. Coronavirus disease 2019 (COVID-19) death rates per million inhabitants in various western and eastern European countries (April 17, 2020). (Reproduced with permission from Ref. 1.)

expression of antioxidant proteins that protect the cell against oxidative damage.³ Fermented vegetables, *e.g.*, cabbage, contain an abundant content of precursors of sulforaphane, the most active natural activator of Nrf2.^{2,3} In addition to sulforaphane, many other micronutrients are required for maintaining immunocompetence by providing an adequate supply of Nrf2-induced antimetabolites, especially vitamins A, C, D, E, and B; iron; selenium; and zinc.⁴⁻¹⁵ Several Nrf2-interacting natural compounds (*e.g.*, berberine, curcumin,^{4,6,16-19} epigallocatechin gallate, genistein, quercetin, resveratrol, sulforaphane) and lactobacilli are also potent Nrf2 activators. It has been proposed that fermented cabbage is a proof-of-concept dietary manipulation that may enhance Nrf2-associated antioxidant effects helpful in mitigating COVID-19 severity.²

WHAT ARE THE PROPOSED MECHANISMS OF ACTION OF NUTRACEUTICALS IN COVID-19 INFECTION?

Because it is rare to find nutraceuticals in adequate quantities in natural foods, to obtain their beneficial antioxidant effects, the field of nutraceuticals has emerged to provide these essential metabolites, which may be deficient in normal diets.² Nutraceuticals are nutrients that

Approved by the Ethical Committee of the University of Verona
 AL Boner is a consultant for Envicon. The remaining authors have no conflicts of interest to declare pertaining to this article
 Address correspondence to Attilio L. Boner, M.D., Via Filippini, 21, Verona, Italy 37121
 E-mail address: attilio.boner@univr.it
 Copyright © 2021, OceanSide Publications, Inc., U.S.A.

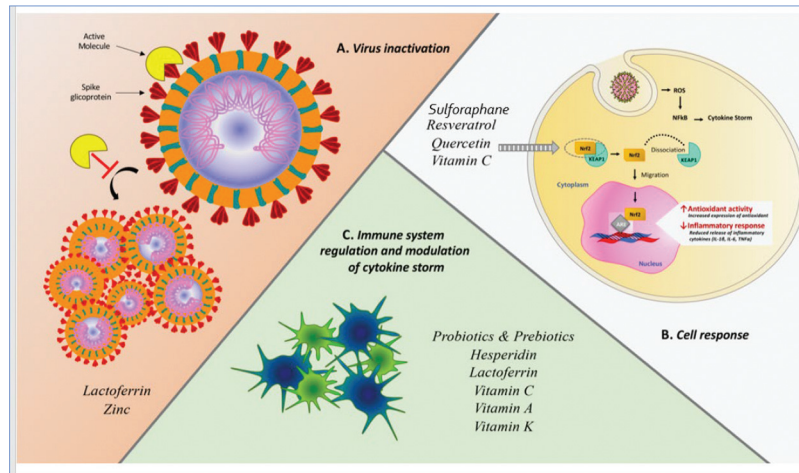


Figure 2. Schematic representation of several mechanisms exploited by nutraceuticals against SARS-CoV-2 infection. (A) Antiviral effects due to the direct interaction with SARS-CoV-2 spike protein or the inhibitory effect of viral proliferation. (B) Cell response induced by the activation of Nrf2 and following genetic regulation downstream. Activated Nrf2 dissociates from its complex with KEAP1 and migrates from cytoplasm to nucleus within which it interacts with ARE sequences and produces gene regulation, both promoting antioxidant response and reducing the inflammatory cascade. (C) Indirect immune system modulation through enhancement of immune performance and the concurrent decrease of proinflammatory cytokines such as IL-6, IL-1 β , and TNF α to mitigate the harmful effects of a cytokine storm. SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; Nrf2 = nuclear factor (erythroid-derived 2) like 2; KEAP1 = Kelch Like ECH Associated Protein 1; ARE = antioxidant response element; IL = interleukin; TNF = tumor necrosis factor. (Modified and reproduced with permission from Ref. 4.)

have beneficial effects on health and consist of a variety of substances that include vitamins, minerals, and herbal products that are extracted, used as food supplements, or added to foods. There are several dietary supplements and nutraceuticals that have been proposed as adjunctive therapies for COVID-19.^{4,6}

The several proposed mechanisms of action of nutraceuticals in COVID-19 infection are shown in Fig. 2 and include the following⁴:

- Antiviral effects due to the direct interaction with SARS-CoV-2 spike protein or the inhibitory effect of viral proliferation.
- Antioxidant effects mediated by the activation of Nrf2, a transcription factor that regulates the expression of antioxidant proteins that protect the cell against oxidative damage triggered by injury and inflammation. *In vitro*, Nrf2 binds to antioxidant response elements in the nucleus, which leads to the transcription of antioxidant response element genes, which produces gene regulation that promotes antioxidant responses and inhibits the inflammatory cascade.³
- Indirect immune system modulatory effects through overall enhancement of immune function and the concurrent decrease of proinflammatory cytokines that mitigate the harmful effects of a cytokine storm such as IL-6, IL-1 β , and TNF α .⁵

A PILOT STUDY OF A NUTRACEUTICAL FOR COVID-19

In a pilot exploratory non-placebo controlled study, the effects of a nutraceutical preparation that contained different combinations of vitamin D, vitamin E, folic acid magnesium, selenium, zinc, curcumin, quercetin, resveratrol, and sulforaphane was evaluated on the transmission of SARS-CoV-2 infections to close contacts. Of 107 subjects who performed a nasopharyngeal swab because of signs and symptoms of respiratory disease, none had a positive results. Of a total of 127 subjects who had nasopharyngeal swabs taken for detection of SARS-CoV-2 by using PCR Test because of close contact with an infected person, 33 of 127 (26%) were positive and 94 of 127 (74%) had negative responses.

Understanding of the transmission of SARS-CoV-2, the virus that causes COVID-19, to close contacts is now an accepted control measure to contain the spread of the virus. Characterization of community exposures, however, can be difficult to assess when widespread transmission is occurring, particularly from persons who are asymptomatic within inherently interconnected communities and among COVID-19 cases without a non-COVID-19 comparison group, as in the present pilot study. However, two studies of transmission of SARS-CoV-2 infections in U.S. households

reported by the U.S. Centers for Disease Control and Prevention (CDC) offers an approximate model for comparison.^{20,21} In contrast to the 26% transmission rate found in the present study, the rate reported among the case patients in the study by Fisher *et al.*²⁰ was 42% (65/154) and in the study by Grijalva *et al.*²¹ was 53% (102/191). Although the present study was a small pilot non-placebo controlled, investigation, these findings lend some support for conducting larger randomized, placebo controlled trials to verify these preliminary results and to establish whether nutraceutical supplementation may offer any benefit in COVID-19 infection.

Michele Piazza, PhD

Paediatric Section, Department of Surgery, Dentistry, Paediatrics, and Gynaecology, University of Verona, Verona, Italy

Attilio L. Boner, MD

Professor Emeritus of Paediatrics Paediatric Section, Department of Surgery, Dentistry, Paediatrics, and Gynaecology, University of Verona, Verona, Italy

Sandro Girotto, MD

Family Practice, Verona, Italy

Ercole Concia, MD

Professor Emeritus of Infectious Diseases Infectious Diseases and Tropical Medicine Section, Department of Diagnostic and Public Health, University of Verona, and Verona, Italy

Joseph A. Bellanti, MD

Professor Emeritus of Paediatrics and Microbiology and immunology Department of Pediatrics and Microbiology-Immunology, Georgetown University Medical Center, Washington, D.C.

REFERENCES

- Bousquet J, Anto JM, Iaccarino G, et al. Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clin Transl Allergy*. 2020; 10:16.
- Bousquet J, Anto JM, Czarlewski W, et al. ARIA group. Cabbage and fermented vegetables: from death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19. *Allergy*. 2021; 76:735–750.
- Bousquet J, Czarlewski W, Zuberbier T, et al. Potential interplay between Nrf2, TRPA1, and TRPV1 in nutrients for the control of COVID-19. *Int Arch Allergy Immunol*. 2021; 10:1–15.
- Parisi GF, Carota G, Castruccio Castracani C, et al. Nutraceuticals in the prevention of viral infections, including COVID-19, among the pediatric population: a review of the literature. *Int J Mol Sci*. 2021; 22:2465.
- Giovinazzo G, Gerardi C, Uberti-Foppa C, et al. Can natural polyphenols help in reducing cytokine storm in COVID-19 patients? *Molecules*. 2020; 25:5888.
- Günelan E, Cebioğlu İK, Çonak Ö. The popularity of the dietary supplements and functional foods in the coronavirus pandemic among the Google users in the USA, UK, Germany, Italy and France. *Complement Ther Med*. 2021; 58:102682.
- Rastogi A, Bhansali A, Khare N, et al. Suri V, Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomized, placebo-controlled, study (SHADE study). *Postgrad Med J*. 2020; postgradmedj-2020-139065.
- Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, et al. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study." *J Steroid Biochem Mol Biol*. 2020; 203:105751.
- Giannini S, Passeri G, Tripepi G, et al. Effectiveness of in-hospital cholecalciferol use on clinical outcomes in comorbid COVID-19 patients: a hypothesis-generating study. *Nutrients*. 2021; 13:219.
- Murai IH, Fernandes AL, Sales LP, et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. *JAMA*. 2021; 325:1053–1060.
- Kaufman HW, Niles JK, Kroll MH, et al. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One*. 2020; 15:e0239252.
- Pereira M, Damascena AD, Galvão Azevedo LM, et al. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2020; 1–9.
- Maghbooli Z, Sahraian MA, Ebrahimi M, et al. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. *PLoS One*. 2020; 15:e0239799.
- Alexander J, Tinkov A, Strand TA, et al. Early nutritional interventions with zinc, selenium and vitamin D for raising anti-viral resistance against progressive COVID-19. *Nutrients*. 2020; 12:2358.
- Jothimani D, Kailasam E, Danielraj S, et al. COVID-19: poor outcomes in patients with zinc deficiency. *Int J Infect Dis*. 2020; 100:343–349.
- Valizadeh H, Abdolmohammadi-Vahid S, Danshina S, et al. Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. *Int Immunopharmacol*. 2020; 89(pt B):107088.
- Saber-Moghaddam N, Salari S, Hejazi S, et al. Oral nano-curcumin formulation efficacy in management of mild to moderate hospitalized coronavirus disease-19 patients: an open label non-randomized clinical trial. *Phytother Res*. 2021; Jan 3. Epub ahead of print.
- Tahmasebi S, El-Esawi MA, Mahmoud ZH, et al. Immunomodulatory effects of nanocurcumin on Th17 cell responses in mild and severe COVID-19 patients. *J Cell Physiol*. 2021; 236:5325–5338.
- Subedi L, Tchen S, Gaire BP, et al. Adjunctive nutraceutical therapies for COVID-19. *Int J Mol Sci*. 2021; 22:1963.
- Fisher KA, Tenforde MW, Feldstein LR, et al. Community and close contact exposures associated with COVID-19 among symptomatic adults ≥18 years in 11 outpatient health care facilities - United States, July 2020. *MMWR Morb Mortal Wkly Rep*. 2020; 69:1258–1264.
- Grijalva CG, Rolfes MA, Zhu Y, et al. Transmission of SARS-CoV-2 infections in households - Tennessee and Wisconsin, April-September 2020. *MMWR Morb Mortal Wkly Rep*. 2020 Nov 6; 69:1631–1634. □